

Remarks/Arguments

The foregoing amendments in the claims are fully supported by the specification as originally filed, and do not add new matter. Specific support for the recitation of an "aqueous solution" in claims 40 and 59 is at least at page 17, lines 21-23 and page 25, lines 5-6 of the specification. Support for the language "by subjecting said conjugate directly, without prior fragmentation and without liberation of the ligand from said conjugate, to mass spectrometry analysis" is, e.g. at page 21, lines 17-25. The further amendments in claim 59 were made and new dependent claims 65-67 added on the analogy of claim 40 and claims dependent thereon, and are supported for the same reason.

Prior to the present amendments, claims 40, 41, 43, 45-50, 59, 60 and 64 were pending in this application, and were rejected on various grounds. Claims 45, 46, 48-50 and 60 have been canceled, without prejudice. New claims 65-67 have been added. The rejection of the remaining claims, including any possible rejection of newly added claims 65-67 on similar grounds, is respectfully traversed.

Applicants appreciate the withdrawal of all previous rejections and objections in view of Applicants' amendments and/or arguments in response to the previous Office Action.

New Rejections

*Objections to the Claims*

Claims 45-46 were objected to as failing to further limit claim 40 from which they depended. The cancellation of claims 45 and 46 moots this objection.

*Claim Rejections - 35 U.S.C. 112, first paragraph*

1. Claims 40-41, 43 and 45-50 were rejected under 35 U.S.C. 112, first paragraph as allegedly containing new matter. According to the rejection, "to the extent that the removal of the phrase 'for identifying a non-oligomeric ligand [that] binds to a target protein wherein said

ligand is less than about 2000 daltons in size' extends to go beyond the original 'purpose' of the method, the increased breadth of possible modification constituted new matter."

The cancellation of claims 45, 46 and 50 moots their rejection. Applicants disagree with and respectfully traverse the rejection of the remaining claims.

The modification that in the Examiner's view constitutes new matter is the simplification of the preamble of claim 40. It is well established that the preamble of a process claim that merely recites the purpose of the claimed process and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone, is not accorded any patentable weight, and is not given the effect of a limitation. *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976), MPEP 2111.02. This is exactly true for claim 40 where the process steps and other limitations recited in the characterizing part of the claim are able to stand alone, and do not require any part of the preamble for completeness. Indeed, all elements of the earlier preamble, e.g. "non-oligomeric ligand" and "less than about 2000 daltons in size," are specifically recited in step (b) of the claimed process. Since under such circumstances the earlier preamble was not given the effect of a limitation, its removal cannot amount to the addition of new matter, or broadening the scope of the claim. Therefore, the withdrawal of the present rejection is respectfully requested.

***Claim Rejections - 35 U.S.C. 112, second paragraph***

Claims 40-41, 43, 45-50, 59-60 and 64 were rejected as "indefinite" for alleged lack of proper antecedent basis for certain terms appearing in the rejected claims.

Claims 45, 46, 50 and 60 have been canceled. The rejection of the remaining claims is respectfully traversed.

A. Claims 40-41, 43, 48, 59 and 60 were rejected since, according to the Examiner, the recitations "the ligand," "the ligand candidates" and "non-oligomeric ligand" had insufficient antecedent basis in these claims.

Step b) of claim 40 has been amended to refer to "said non-oligomeric ligand candidates," using an identical wording with the phrase relied on for antecedent basis. Accordingly, the phrase "said non-oligomeric ligand" has specific support in the previous part of step b).

Step c) of claim 40 has been amended to eliminate the phrase "non-oligomeric." Claim 40, as amended, does not contain the recitation "the ligand" in isolation. Rather, the full cite states: "the ligand present in said target protein-ligand conjugate." Proper and complete antecedent basis for the latter term is provided in step b) of the claim.

Similar amendments were made in claim 59.

In view of the current claim amendments and explanation, the Examiner is respectfully requested to withdraw the present rejection.

B. Claim 64 was rejected as "vague and indefinite" in its recitation of the term "associated." The current amendment of claim 64, to recite that the -SH group is "part of" as cysteine residue is believed to overcome this rejection.

C. Claim 59 was rejected for the recitation of "the covalent target protein-ligand conjugate" in step c). All claims dependent on claim 59 were rejected for the same reason. Step b) of claim 59 has been amended to recite a "covalent target protein-ligand conjugate," which provides proper antecedent basis for the recitation of the same phrase in step c). Accordingly, the Examiner is requested to withdraw the present rejection.

***Claim Rejections - 35 U.S.C. § 102***

Claims 40-41, 43, 45-46, 59 and 64 were rejected as allegedly being anticipated by Kim et al. (WO 98/11436; March 19, 1998).

Kim et al. describes a method of detecting a ligand that binds to a target molecule. The ligand and the target molecule each contains, as obtained or modified, a member of a binding pair, to permit covalent linkage or tethering of the ligand when bound to the target molecule. In one embodiment, the binding pair consists of sulphydryl groups. Kim et al. does not teach the use of mass spectrometry for identifying the ligand present in the target protein-ligand candidates. Since Kim et al. fails to teach at least one element of the claimed method, it does not anticipate any of the rejected claims, and the present rejection should be withdrawn.

***Claim Rejection - 35 USC § 103***

Claims 40-41, 43, 45-50, 59-60, and 64 were rejected under 25 U.S.C. 103(a) as "obvious" over Kim et al. and Siuzdak. Kim et al. was erroneously identified as U.S. Patent No. 5,367,058. Applicants will, however, treat the rejection as if it had properly referred to WO 98/11436. Claims 45, 46, 48-50, and 60 were canceled, which moots their rejection. The rejection of the remaining claims is respectfully traversed.

As discussed in response to the previous rejection Kim et al. does not teach the use of mass spectrometry (MS) for the detection and identification of a ligand present in a target protein-ligand candidate. Indeed, a serious deficiency of Kim et al. is its failure to sufficiently teach the identification of a ligand bound to a target molecule by methods other than the formation of ligand-target molecule complexes with ligand candidates displayed on beads, removal of any non-covalently bound target molecule, and detection of beads by antibody binding detection methods. (Paragraph bridging pages 19-20.) Other than this very specific scenario, the disclosure of Kim et al. offers generic statements only, such as: "Specific binding of a target molecule and a potential ligand tethered thereto is determined (and, thus, a ligand of the target molecule is identified), using known methods." (Page 14, lines 6-9) There is no teaching or disclosure that would elaborate on such "known methods."

The Examiner cited Siuzdak for its teaching of electrospray mass spectrometry, which is said to have "demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction," which, in the Examiner's reading, "would encompass the 'antibody-antigen' complexes disclosed by Kim et al." The Examiner adds that there would have been a motivation to combine the teaching of Kim et al. with Siuzdak, since "Siuzdak explicitly states that electrospray has 'demonstrated its potential' for these systems."

First of all, Siuzdak does not explicitly state that electrospray mass spectrometry has demonstrated its potential for identifying ligands present in a covalent conjugate between a target protein and a ligand of the protein. The quoted sentence is limited to the observation of covalent-bound intermediates in an antibody-catalyzed reaction. Observing a chemical entity, such as a protein-bound intermediate, and determining the identity of such chemical entity are

two very different things. Accordingly, Siuzdak et al. does not provide the motivation relied upon by the Examiner.

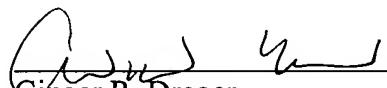
Secondly, even if Kim et al. and Siuzdak had been properly combined, the combination would still not make obvious the invention as presently claimed. The claims require determination of the identity of a ligand present in a target protein-ligand conjugate "by subjecting said conjugate directly, without prior fragmentation and without liberation of the ligand from said conjugate, to mass spectrometry analysis." Such method is not disclosed or suggested by Siuzdak, therefore, its combination with Kim et al. does not make obvious the claims currently pending.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Respectfully submitted,

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